

PATENT COOPERATION TREATY

Rec'd PCT/PTO 10 JUL 2004 PCT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)



REC'D 03 MAY 2004

Applicant's or agent's file reference 27196P WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP 03/00504	International filing date (day/month/year) 20.01.2003	Priority date (day/month/year) 18.01.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/415		
Applicant THE GENETICS COMPANY INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
 - ☒ This report is also accompanied by/ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 31.07.2003	Date of completion of this report 30.04.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Loher, F Telephone No. +49 89 2399-7839 <div style="text-align: right;">  </div>

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/00504**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-30 as originally filed

Claims, Numbers

1-12 received on 28.01.2004 with letter of 28.01.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/00504**

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-10 and 12 (partially N,IS); 11 (IA)

because:

☒ the said international application, or the said claims Nos. 11 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-10 and 12 (partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	2,5-11
	No: Claims	1,3,4,12
Inventive step (IS)	Yes: Claims	2,5,7-11
	No: Claims	1,3,4,6,12
Industrial applicability (IA)	Yes: Claims	1-10 and 11
	No: Claims	

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP03/00504

Re Item I

Basis of the report

The examination is being carried out on the following application documents:

Text for the Contracting States:

AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL
PL PT RO SE SI SK TR

Description, pages:

1-30 as originally filed

Claims, No.:

1-12 as received on 28/01/2004 with letter of 28/01/2004

Art 34(2)(b) The amendments filed with the letter dated 28/01/2004 do not introduce subject-matter which extends beyond the content of the application as filed. Therefore, the requirements of Article 34(2)(b) PCT are met.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Concerning present claims 1-12 it is noted that an incomplete search report has been established.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to subject-matter in respect of which no international search report has been established are not subject of an international preliminary examination (Rule 66.1(e) PCT).

Consequently, the examination has been carried out for those parts of the claims relating to the composition disclosed in the examples (i.e. the compounds ID1-ID7 disclosed in claim 2 and compounds with alleged beta secretase inhibitory action which fall within the scope of formula (I)).

Claim 11 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Art 6 The attention of the applicant is drawn to the fact that there are substantial defects within the application as filed that a lack of clarity within the meaning of Article 6 PCT arises. Amended claim 6 refers to a substance library. The term "substance library" lacks a well-recognized meaning. Even after reading the definition given in the description on page 13f it is not clear, whether the term "library" relates to a mixture type or an array type or both.

Art 33(2) The present application does not meet the requirements of Article 33(2) PCT, since the subject-matter of amended claims 1, 3, 4 and 12 is not new.

D1 discloses compound ID5 (tautomer) mentioned in amended claim 12 of the present application. Therefore, the subject-matter of amended claim 12 is not new in the light of D1.

D5 (XP2240136) discloses a compound falling within the scope of the Markush formula of amended claim 1. Implicitly the compound will have the properties claimed in amended claims 3 and 4 of the present application. Therefore the subject-matter of said claims is not new in the light of D5.

Art 33(3) The present application does not meet the requirements of Article 33(3) PCT, since the subject-matter of claims 1, 3, 4, 6 and 12 does not seem to involve an inventive step.

D2, which is considered to represent the most relevant state of the art, discloses a Markush formula and specific compounds for the treatment of Alzheimer's disease and other diseases caused by beta amyloid protein. The main compound falls within the scope of the Markush formula disclosed on page 4 of the present application.

The problem to be solved by the present invention may therefore be regarded as how to provide compounds which are beta secretase inhibitors suitable for the treatment of beta-amyloid-related neurodegenerative diseases such as Alzheimer's disease.

The present application suggests to solve the problem posed by providing compounds covered by Markush formula (1) and compounds ID1-ID7 which are capable of inhibiting beta secretase and are, therefore, suitable for the treatment of Alzheimer's disease, Down syndrome and several other amyloid neuropathies.

Taking into account the teaching of the cited prior art the following reasoning applies:

With respect to the subject-matter of amended claims 1, 3, 4 and 12 the applicant's attention is drawn to the fact that even if novelty could be established over the above-cited prior art it is at present not clear wherein an inventive step may reside.

With respect to amended claim 7 the following reasoning applies: The application as filed lacks evidence that the problem of providing a substance library containing at least 5 beta-secretase inhibitors according to the Markush formula of amended claim 1 has been solved. The present application merely discloses two compounds falling within the scope of said formula (i.e. ID6 and ID7). Consequently, this formulation covers future inventions. Therefore the claim would not unduly be limited by restricting it to disclosed compounds, since it is not an undue limitation of the claim to eliminate what has not yet been invented.

With respect to the subject-matter of claims 2, 5, 7, 8, 9, 10 and 11 inventive step is acknowledged. Compounds ID6 and ID7 have not been disclosed by the prior art in time. Neither does prior art disclose a pharmaceutical composition comprising a compound falling within the scope of the Markush formula of amended claim 1. The application provides evidence that said compounds are effective beta secretase inhibitors and might therefore be suitable for the treatment of beta-amyloid-related neurodegenerative diseases. This teaching could not have been derived from the prior art. In conclusion, the subject-matter of claims 2, 5, 7, 8, 9, 10 and 11 is inventive in the sense of Article 33(3) PCT.

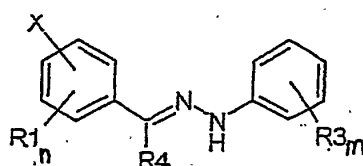
Art 33(4) The subject-matter of claims 1-10 and 12 is considered to be industrially applicable in the sense of Art 33(4) PCT.

For the assessment of the present claim 11 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

International Patent Application
No. PCT/EP03/00504
The Genetics Company Inc.
27196P WO/MDBCmh

New Claims

1. Beta-secretase inhibitor of formula (1)



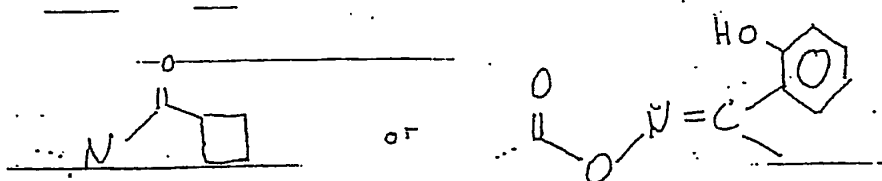
wherein

X: represents a halogen or a moiety which is bioisosteric thereto, in particular, F, Cl, Br, I, Methyl or CF₃, preferably Cl.

R1: each independently represents halogen, hydroxy, cyano, trifluoromethyl, nitro, a hydrocarbon group containing 1 to 4 carbon atoms, in particular, C1-C4 alkyl, C2-C4 alkenyl or C2-C4 alkynyl, which may be substituted, e.g. hydroxyalkyl, haloalkyl, cyanoalkyl, carboxyalkyl, acylalkyl, oxyalkyl, sulfonylalkyl, sulfonylamidoalkyl, amidoalkyl, carbonylalkyl, ureylalkyl, etc. or a moiety which is bioisosteric thereto and $n = 0$ to 2.

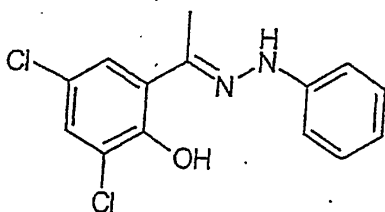
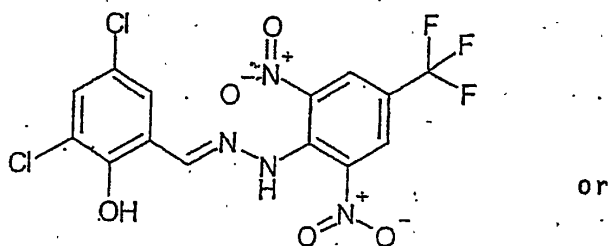
R3: each independently,

selected from R1 or is a aryl or heterocyclic moiety substituted by 0 to 4 moieties from R1 or a group selected from



R4: represents halogen, hydroxy, cyano, trifluoromethyl, C1-C4 alkyl, C2-C4 alkenyl or C2-C4 alkynyl which may be substituted, e.g. hydroxyalkyl, haloalkyl, cyanoalkyl, carboxyalkyl, acylalkyl, oxyalkyl, sulfonylalkyl, sulfonylamidoalkyl, amidoalkyl, carbonylalkyl, ureylalkyl, etc. or a moiety which is biosteric thereto and $m = 0$ to 4.

2. Beta-secretase inhibitor according to claim 1 having the formula



3. Beta-secretase inhibitor according to claim 1 or 2, having an $IC_{50} \leq 200 \mu M$.
4. Beta-secretase inhibitor according to any of claims 1 to 3, being active in cells.

5. A pharmaceutical composition comprising a beta-secretase inhibitor according to any of claims 1 to 4, optionally in admixture with one or more pharmaceutically acceptable carriers, diluents and/or excipients.
6. A substance library containing at least 5 beta-secretase inhibitors according to any of claims 1 to 4,
7. The use of a beta-secretase inhibitor according to any of claims 1 to 4 for the manufacture of a pharmaceutical agent for the treatment or prevention of a condition which is mediated by beta-secretase.
8. The use of a beta-secretase inhibitor according to any of claims 1 to 4 for the manufacture of a pharmaceutical agent to inhibit the formation of beta amyloid peptides from the amyloid precursor protein (APP).
9. The use according to claim 7 or 8 for the manufacture of a pharmaceutical agent for the treatment or prevention of Alzheimer's disease or any disorder caused by pathological deposits of beta amyloid peptides.
10. Use of a beta-secretase inhibitor according to any of claims 1 to 4 in the manufacture of a pharmaceutical agent for the treatment or prevention of conditions selected from the group consisting of Alzheimer's disease, Down syndrome, cerebral amyloid angiopathy, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch type (HCHWA-D) and other degenerative dementia characterized by beta-amyloid deposits.

11. A method of treating or preventing a disease characterized by beta-amyloid deposits such as Alzheimer's disease by modulating the activity of the beta-amyloid converting enzyme, comprising administering to a patient in need of such treatment a compound according to claims 1 to 4, or a pharmaceutically acceptable salt thereof.

12. Beta-secretase inhibitor having the formula

